REMARKS

Amendment to the Specification

The specification is amended to change the title to one which is more indicative of the claims to which the invention is directed, as requested by the Examiner. This amendment introduces no new matter into the application.

Status of and Amendments to the Claims

Claims 1, 4-6, 8-9, and 22-27 are amended herein, and new claim 34 is added herein. To expedite prosecution, claims 7, 10-21, and 28-33 are canceled herein without prejudice to renewal or to filing in a continuation or divisional application. Claims 1-6, 8-9, 22-27 and 34 are pending with entry of this amendment, with claim 34 drawn to a non-elected invention.

Please note that Applicants reserve the right to reinstate or to file subsequent applications claiming any of the canceled subject matter, and that the claim amendments and cancellations should not be construed as abandonment of any presently or previously claimed subject matter or agreement with any objection or rejection of record.

Claim 1 is amended to introduce the limitations of claim 7 (which is canceled herein), and to clarify claim language. Support for "a variant of hG-CSF with an amino acid sequence which differs in 1-8 amino acid residues from SEQ ID NO:1" in claim 1 may be found, for example, at least on page 24 lines 1-14. For clarity, claim 1 is also amended to recite the term "linker peptide" rather than "peptide linker", support for which is found, for example, at least on page 18 line 17-page 19 line 27.

Claims 4-6, 8-9, and 22-27 are amended for clarity and/or to conform with the claim(s) from which they depend. New claim 34 is drawn to a method of treatment using the polypeptide of claim 1, support for which may be found, for example, at least on page 28 lines 10-32, page 82 line 15- page 83 line 10, and original claim 28. A request for rejoinder of this method claim in accordance with 35 USC §121 follows. The claim amendments and the new claim introduce no new matter into the application.

Request for Rejoinder Pursuant to MPEP §821.04

Method claim 34, drawn to non-elected invention group II according to the Requirement for Restriction dated December 11, 2003, incorporates all of the limitations of product claim 1. In accordance with 35 USC §121 and MPEP §821.04, Applicants request that claim 34 be rejoined and examined in the instant application upon a finding of allowablity of the product claim from which it depends.

Information Disclosure Statement

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statements which were submitted by Applicants on February 13, 2002 (including a five-page Form 1449 citing references numbered 1-88) and on May 28, 2002 (including a one-page Form 1449 citing references designated AA-AB), as evidenced by the initialed and signed copies of the above-noted Forms 1449 included with the Office Action.

Objection the Specification

The Examiner required a new title more descriptive of the claimed invention. The title of the instant application has been changed to "Single-Chain G-CSF Polypeptides", as suggested by the Examiner.

Rejection under 35 USC §112 first paragraph

Claim 1-6, 8-11, 14-17, 20-27, and 29-32 were rejected under 35 USC 112 first paragraph for allegedly being non-enabling with respect to the scope of the claims. Claims 10-11, 14-17, 20-21 and 29-32 have been canceled, rendering the rejection of these claims moot. The rejection of pending claims 1-6, 8-9, and 22-27 is respectfully traversed.

The Office Action alleges that claim 1 is overly broad in its limitation of "variants of G-CSF" because no upper limit is provided in the claim regarding the number of modifications and no guidance is provided in the specification as to how one of skill would generate a hG-CSF

variant, other than those recited in claim 7. It was noted in the Office Action that the specification is enabling for single-chain multimeric polypeptides comprising hG-CSF monomers of amino acid sequence that differs from that set forth in SEQ ID NO:1 by an amino acid modification as set forth in claim 7 or 13. Claim 1 is amended herein to further define a variant of hG-CSF by incorporating the limitations of claim 7 and to provide an upper limit to the number of modifications in said variant. Pending claims 2-4, 6, 8, 9, and 22-27 incorporate these limitations by virtue of their dependence from claim 1. As the Examiner had also noted in the Office Action that the specification is enabling for single-chain multimeric polypeptides comprising hG-CSF protein monomers set forth in SEQ ID NO:1, it is believed that claim 5 is also enabled.

In light of the above, Applicants submit the pending claims are enabled and respectfully request the rejection under 35 USC §112 first paragraph be withdrawn.

Rejection under 35 USC §112 second paragraph

Claims 1-27 and 29-33 were rejected under 35 USC §112 second paragraph as allegedly indefinite. This rejection is respectfully traversed in view of the pending claims.

Claims 1, 9, 10, 29 and 31 were considered vague and indefinite owing to the recitation of the term "variant". Claims 10, 29 and 31 are canceled rendering rejection of these claims moot. Claim 1 is amended herein to the clarify the metes and bounds of this term. Claim 9 incorporates the limitations of amended claim 1.

Claims 4, 5, and 8 were considered confusing owing to the use of brackets (actually, parentheses) surrounding the term "SEQ ID NO:1". These claims have been amended as suggested by the Examiner to recite the phrase "as set forth in SEQ ID NO:1". For consistency, claim 1 has likewise been amended to recite this phrase.

Claims 10, 20 and 21 have been canceled, rendering the rejection of these claims moot.

Claim 22 is amended to recite a "nucleic acid comprising a nucleotide sequence" as suggested by the Examiner.

Claims 23 has been amended to recite "an expression vector comprising the nucleic acid", and claim 25 has been amended to depend from claim 23. It is believed these claims as amended are clear and definite.

It is believed that pending claims 2-3, 6, 8, 24, 26, and 27 are likewise clear and definite insofar as they incorporate the limitations of the claims as amended above.

In light of the above, it is believed all the claims pending in this application are clear and definite. Applicants therefore request the rejection under 35 USC §112 second paragraph be withdrawn.

Rejection under 35 USC §103(a)

Claims 1-27 and 29-33 were rejected under 35 USC § 103(a) as allegedly being unpatentable over US Patent 5,824,778 issued to Ishikawa *et al.* (hereinafter "Ishikawa") in view of WO 99/38891 (hereinafter "Sytkowski"). Of the rejected claims, claims 7, 10-21, and 29-33 have been canceled herein, rendering the rejection of these claims moot. The rejection of pending claims 1-6, 8-9, and 22-27 is respectfully traversed.

Applicants respectfully submit that the Office Action has not established a *prima facie* case of obviousness of the claims based on the teachings of Ishikawa in view of Sytkowski. According to the MPEP at §2143, to establish a *prima facie* case of obviousness, at a minimum there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, and there must be a reasonable expectation of success. Furthermore, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the cited art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP §2143.03 further states that if an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious.

Claim 1 is directed to a single-chain multimeric polypeptide having G-CSF activity, comprising at least two monomeric units independently selected from (a) hG-CSF with the amino acid sequence as set forth in SEQ ID NO:1 and (b) a variant of hG-CSF with an amino

acid sequence which differs in 1-8 amino acid residues from SEQ ID NO:1 and which comprises at least one amino acid residue modification selected from the group consisting of: introduction of a lysine, cysteine, aspartic acid, glutamic acid or histidine residue, and removal of a lysine, cysteine, aspartic acid, glutamic acid or histidine residue, said monomeric units being linked via a peptide bond or a linker peptide, the polypeptide comprising at least one covalently bound polymer molecule selected from the group consisting of a linear polyalkylene oxide and a branched polyalkylene oxide. All of the remaining pending claims depend from and incorporate the limitations of claim 1.

There is no motivation to combine the cited references to arrive at the claimed invention

The Examiner asserts that it would have been obvious to one of ordinary skill to modify the hG-CSF polypeptide of Ishikawa such that it includes multimers of monomeric hG-CSF bonded to PEG to obtain a multimeric hG-CSF protein with an increased circulating half-life as taught by Sytkowski. The Examiner stated that since "cytokines such as G-CSF are well known in the art as having a short half-life ... it would have been obvious to obtain multimers of the hG-CSF protein conjugated to PEG, to improve the therapeutic potential of hG-CSF", and that "[o]ne would have been motivated to obtain multimers comprising hG-CSF and PEG to decrease its clearance *in vivo* and also since the multimer protein would have greater biological activity than the same amount of hG-CSF alone", allowing lower doses of hG-CSF to be used therapeutically.

Applicants respectfully submit that the Examiner fails to recognize that Sytkowski actually teaches away from PEGylation as a means for increasing the biological activity of proteins. In the "Background of the Invention" (pages 1-2) Sytkowski discusses some known methods for modification of naturally occurring polypeptides in an effort to increase their biological activity. One of the methods discussed is to increase the size of a protein by chemical conjugation with a reagent such as polyethylene glycol (PEG); see page 1 lines 12-24. At the top of page 2 Sytkowski warns, however, that "the conjugation of chemical compounds or inert molecules to a polypeptide often results in a significant decrease of the overall biological activity, and of selected biological activity of the polypeptide". The invention of Sytkowski,

wherein polypeptide monomers are linked together via a heterobifunctional crosslinking reagent to form multimeric polypeptides, is presented as an *alternative* method to e.g. PEGylation with the aim of producing modified polypeptides with increased biological activity. Given that Sytkowski is clearly aware of PEGylation as a means for increasing the size of a protein, it is significant that he makes no suggestion whatsoever that the multimeric EPO polypeptides described therein might also be subjected to conjugation with PEG. This fact, together with the fact that Sytkowski warns against the decrease in overall biological activity that may result from PEGylation, shows that the cited references clearly do not provide the requisite desirability of the combination. One skilled in the art would not have been motivated to combine the teachings of Sytkowski with the teaching of Ishikawa to arrive at the claimed invention.

For at least the reasons discussed above, Applicants respectfully submit that, at a minimum, one skilled in the art would not be motivated to combine the teachings of Ishikawa and Sytkowski to arrive at the claimed invention, and as such a *prima facie* case of obviousness has not been established over Ishikawa in view of Sytkowski.

The cited references provide no reasonable expectation of success

The Examiner asserts that " [w]ith respect to claims 10, 20 and 21 there would be a reasonable expectation of success by one of skill in the art based on the above references and that an *in vitro* bioactivity in the range of about 2-30% of the bioactivity of non-conjugated hG-CSF would be obtained because of the size of the PEG molecules which affects the biological activity of hG-CSF (steric hindrance caused by the molecular weight of PEG which masks the active site of hG-CSF)." (Office Action, page 9, lines 3-7).

The Examiner is respectfully reminded that the reasonable expectation of success must be found in the cited art, not in Applicant's disclosure. Furthermore, claims 10, 20 and 21 have been canceled herein, rendering this assertion moot. As was noted above, Sytkowski teaches away from the combination of multimerization and PEGylation, and Ishikawa is silent on the concept of multimerization. For at least these reasons, Applicants respectfully submit that the combination of Ishikawa and Sytkowski provides no reasonable expectation that one of skill could successfully practice the invention as claimed in independent claim 1 or claims which

depend therefrom, and as such a *prima facie* case of obviousness has not been established over Ishikawa in view of Sytkowski.

In conclusion, Applicants respectfully submit that a *prima facie* case of obviousness has not been established in the rejection of independent claim 1, and claims which depend therefrom, over Ishikawa in view of Sytkowski. Therefore, Applicants respectfully request the rejection of pending claims 1-6, 8-9, and 22-27 under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe the claims pending in this application are in condition for allowance. Early notification to that effect is earnestly solicited. As noted above, prior to conclusion of prosecution on the merits in this application, Applicants request rejoinder of the currently withdrawn method claims.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 298-5452.

Respectfully submitted,

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